Response to: 'Association between osteoporosis and statin therapy: the story continues' by Burden and Weiler

We have read with great interest the correspondence of Burden and Weiler[1] referring to our previously published manuscripts.[2 3] First, they sharply observe that the crude OR between the statin group and the matched cohort shows no effect and therefore inquire as to how exactly we adjust for age. In our original study, we grouped patients according to their medications, computed mean age and sex within these medication groups as covariates, and performed a weighted multivariate regression on the risk of osteoporosis within the different medication groups (one 'observation' corresponds to one medication group, weighted proportionally to the patients in that group). This grouping by medication was performed for computational convenience due to our large cohort. We confirmed that our results do not qualitatively change if instead of grouping the patients we evaluate a regression model in which each observation is one patient. In response to the correspondence by Burden and Weiler, we have now additionally performed a multivariate regression as reported in the original paper, except that we used the 'matched cohort' as the control group rather than all patients without statins. This change in the reference group did not qualitatively affect the results either. Using the matched cohort, we observed an OR of 0.83 (95% CI 0.76to 0.91) for 0–10 mg simvastatin, 0.98 (CI 0.94 to 1.03) for 10–20 mg, 1.26 (CI 1.19 to 1.32) for 20–40 mg, 1.92 (CI 1.71 to 2.16) for 40–60 mg and 3.82 (CI 2.88 to 5.07) for 60–80 mg. These results render it highly unlikely that age was a potential confounding factor. Note that the distribution of patients over these dosage groups is uneven, with 53% of patients having dosages between 0 and 20 mg, 39% dosages of 20–40 mg and 8% with >40 mg. Therefore, if we pool all patients in one group, the risk-decreasing or neutral association in the low-dosage patients 'cancels out' the risk increase of higher dosages, resulting in the observed balanced crude OR.

Statins are among the most prescribed medications worldwide. The main mechanism of statins is inhibition of hydroxymethylglutaryl-CoA (HMG-CoA) reductase, which in further consequence reduces the synthesis of cholesterol.[4] Cholesterol is the basic substance for the synthesis of vital hormones such as cortisol or sex hormones. Our cross-sectional study was the first to investigate different types of statins and their dosages in detail, although earlier studies showed that statins could reduce sex hormone levels.[5–9] Thus we have hypothesised that the higher potencies and dosages of statins and their stronger cholesterol-lowering effect could inhibit the synthesis of vital hormones such as sex hormones more strongly and, therefore, be related to associated diseases such as osteoporosis. Our results show that dosages of 0–10 mg of pravastatin were related to a 32% decreased risk of being diagnosed with osteoporosis when compared with controls—similar results could be observed for the low-potency statin lovastatin. Interestingly, there was no significant overrepresentation of diagnosed osteoporosis in higher dosages of pravastatin or lovastatin. The first significant overrepresentation of osteoporosis in statin-treated patients could be observed in higher dosages of 40–60 mg of simvastatin and thus there was a 64% higher risk of being diagnosed with osteoporosis. In their correspondence, Burden and Weiler make the point that—following our hypothesis—effects observed for simvastatin with dosages >40 mg should be comparable to 20 mg atorvastatin and 10 mg rosuvastatin. Indeed, for atorvastatin 10–20 mg (20–40 mg) we found an OR of 1.35 (1.78). Both ORs are within the confidence intervals of simvastatin 40–60 mg (1.64, CI 1.31 to 2.07); hence these results are comparable. For even higher dosages, results should be interpreted with care because of the decreasing sample sizes and the increasing CIs. Results for rosuvastatin are at present not conclusive with respect to the impact of statin potency. For 20–40 mg we observed an OR of 2.04 with a relatively large CI of 1.31 to 3.18. For even higher dosages, sample sizes were not sufficient to obtain results. Findings for rosuvastatin should therefore be interpreted with care, particularly as—in contrast to simvastatin and atorvastatin—it is not metabolised by CYP3A4,[10 11] which is also mainly involved in the metabolisation of sex hormones such as oestrogen.[12–14] Because of the cross-sectional study design, at present we cannot establish potential time-ordering between the beginning of statin treatment and onset of osteoporosis. It therefore goes without saying that we are only able to report correlations and not causative interactions. We were able to exclude potential confounding factors such as age (as described above), sex and certain comorbid diseases (eg, rheumatoid arthritis, ischaemic heart disease, stroke, diabetes, nicotine dependency or overweight and obesity), in order to rule out confounding by indication stemming from these diagnoses. These robustness tests did not change our results qualitatively. Nevertheless, large prospective studies are certainly needed in order to validate our recently proposed mechanism of the possible inhibiting effect of statins on sex hormones.

Michael Leutner,[1] Caspar Matzhold,[2,3] Luise Bellach,[1] Carola Deischinger,[1] Jürgen Harreiter,[1] Stefan Thurner,[2,3,4,5] Peter Klimek,[2,3] Alexandra Kautzky-Willer [1]

[1]Department of Internal Medicine III, Clinical Division of Endocrinology and Metabolism, Unit of Gender Medicine, Medical University of Vienna, Vienna, Austria
[2]Section for Science of Complex Systems, CeMSIIS, Medical University of Vienna, Vienna, Austria
[3]Complexity Science Hub Vienna, Vienna, Austria
[4]Santa Fe Institute, Santa Fe, NM, USA
[5]IIASA, Laxenburg, Austria

Correspondence to Professor Alexandra Kautzky-Willer, Internal Medicine III, Division of Endocrinology and Metabolism, Unit of Gender Medicine, Medical University of Vienna, Vienna, Austria; alexandra.kautzky-willer@meduniwien.ac.at

Contributors ML, CM, ST, PK and AK-W were involved in the study design. ML, CM, PK were involved in the data analysis. ML, CM, PK and AK-W performed manuscript writing. All authors read, reviewed and approved the final response to the correspondence.

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ORCID iD
Alexandra Kautzky-Willer http://orcid.org/0000-0002-3520-4105

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